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DESIGN OF REACTION MEDIA FOR NUCLEOPHILIC SUBSTITUTION REACTIONS BY USING A CATALYTIC AMOUNT OF AN AMPHIPHILIC IMIDAZOLIUM SALT IN WATER

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This paper is dedicated to Professor Dr. Akira Suzuki as we celebrate his 80th birthday.

Abstract – Molecules of an amphiphilic imidazolium salt assemble in water to form a hydrophobic membrane including an interface consisting of ammonium species. Such an interface works as a reaction medium like an ionic liquid. We used the medium for nucleophilic substitution reactions between alkyl halides and anionic nucleophiles. This procedure allowed the reactions to proceed efficiently in water without any organic solvent.

INTRODUCTION

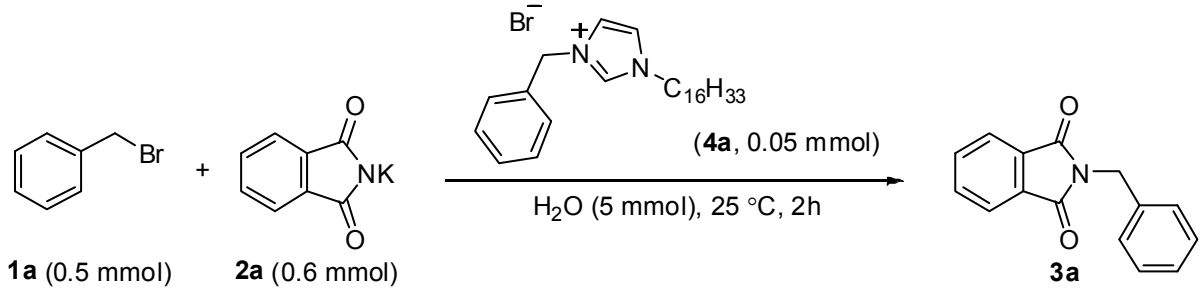
Reactions using ionic liquids as a solvent have received considerable attention.[1,2] The unique properties of ionic liquids, such as high polarity, non-coordinating nature, nonvolatility, and anisotropic aspects, provide several benefits for organic reactions, including reactions with polar organic compounds[3] or gases,[4,5b–d] organometallic reactions,[5] and even biocatalytic reactions.[2f,6] However, there are also some problems, which include the difficulty of isolating the product and the high cost for reaction media.[1]

To overcome such problems while keeping the merits, we focused on the amphiphilicity of imidazolium salts with a hydrophobic long hydrocarbon chain.[7-9] The use of an amphiphilic imidazolium salt in water will align the molecules to construct an interface between water molecules and organic compounds efficiently, and the interface might be a practical reaction medium for the

reactions mentioned above.[7-11] In this manuscript we describe nucleophilic substitutions performed in the medium constructed by a catalytic amount of imidazolium salts in water.[2]

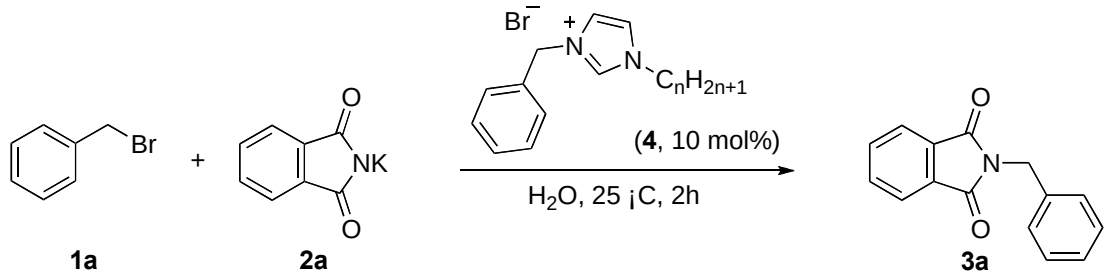
RESULTS AND DISCUSSION

We examined the reaction between benzyl bromide (**1a**) and phthalimide potassium salt (**2a**) using 10 mol% of 1-hexadecyl-3-phenylmethyl-1*H*-imidazolium bromide (**4a**) in water (Scheme 1). The reaction gave *N*-benzylphthalimide (**3a**) in 96% yield. When the reaction was examined in the absence of **4a**, only a trace amount of the product was obtained. Water is also essential for this reaction; in the absence of water, the rate of the reaction became slower. The combination of **4a** and water was shown to be indispensable for the efficient reaction.



Scheme 1. Nucleophilic substitution reaction between **1a** and **2a**

Table 1. Nucleophilic substitution reaction in water between **1a** and **2a** in the presence of imidazolium salts (**4**) having an alkyl chain as a hydrophobic group[a]

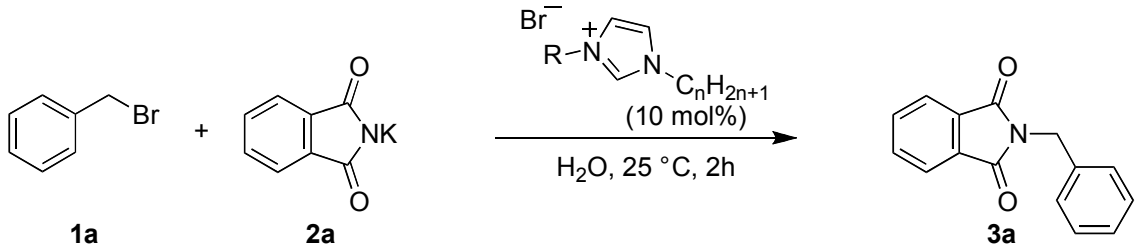


Entry	**n**		Yield (%)[b]
1	1	(**4b**)	18
2	4	(**4c**)	36
3	10	(**4d**)	96
4	16	(**4a**)	96

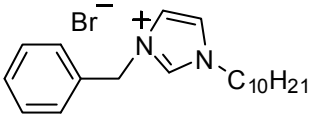
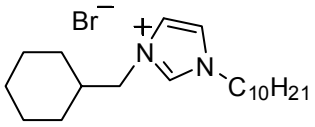
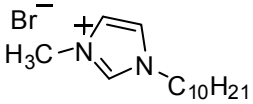
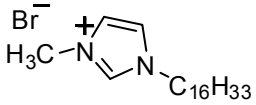
[a] **1a** (0.5 mmol), **2a** (0.6 mmol), **4** (0.05 mmol), and H_2O (5.0 mmol) were used for the reaction.
[b] Determined by ^1H NMR.

The lengths of an alkyl chain on 1-alkyl-3-phenylmethyl-1*H*-imidazolium bromide (**4**) were arranged from C1 to C16 (Table 1). Among them, imidazolium salts (**4a**, **4d**) with the alkyl chain (C10 and C16) afforded the desired product (**3a**) in good yields (Table 1, entries 3 and 4).

Table 2. Effect of the substituent on imidazolium salts (**4**–**6**) for the nucleophilic substitution reaction in water between **1a** and **2a**[a]



1a **2a** **3a**

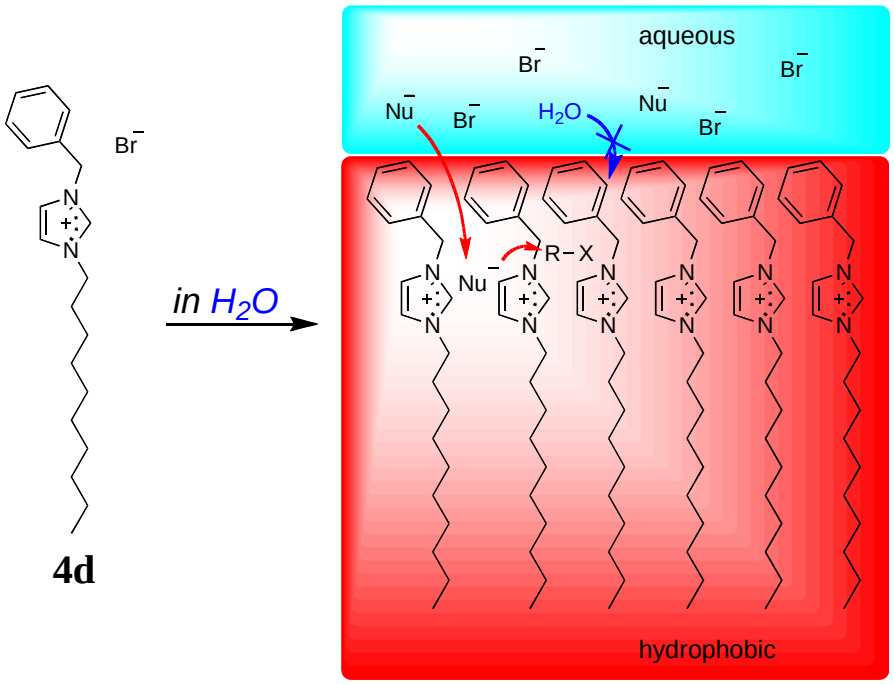
Entry	**Imdazolium salt**		Yield (%)[b]
1		(**4d**)	96
2		(**5**)	96
3		(**6a**)	37
4		(**6b**)	44

[a] **1a** (0.5 mmol), **2a** (0.6 mmol), **4**–**6** (0.05 mmol), and H_2O (5.0 mmol) were used for the reaction.
[b] Determined by ^1H NMR.

Then we examined the effect of the second substituent in the imidazolium salts (Table 2). 1-Decyl-3-cyclohexylmethyl-1*H*-imidazolium bromide (**5**) was effective for this reaction to the same degree as **4d** (Table 2, entries 1 and 2), but 1-decyl-3-methyl-1*H*-imidazolium bromide (**6a**) was less effective (Table 2, entry 3). Even when the alkyl chain was longer than that of **6a**, the yield was still low (Table 2, **6b**, entry 4). These results suggest that **4d** or **5** assembles in water to form an aggregation including a "hydrophobic cationic layer" in which the reaction proceeds (Scheme 2), but in the case of **6a** or **6b**, the imidazolium part may not be hydrophobic enough to perform an organic reaction of the substrate (**1a**).

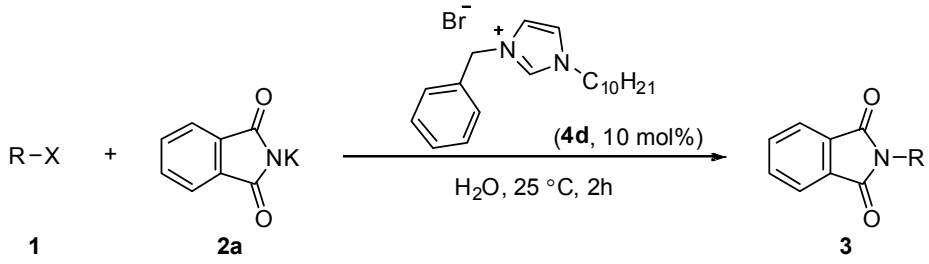
We also investigated the reactions of phthalimide potassium salt (**2a**) with the other electrophiles (**1b**–**1k**) by using **4d** (Table 3). Allylic and propargylic bromides (**1b**–**1e**) underwent the reaction to give the corresponding products (**3b**–**3e**) in moderate to good yields (Table 3, entries 1–4), while a non-activated octyl bromide (**1f**) and mesylate (**1f'**) were poorly reactive (Table 3, entries 5 and 6). Reactions with α-bromoesters (**1g**–**1k**) also took place efficiently to produce the corresponding α-amino acid derivatives (Table 3, **3g**–**3k**, entries 7–11). Especially, *tert*-butyl bromoacetate (**1h**) was highly reactive under the condition to give a glycine derivative (**3h**) quantitatively (Table 3, entry 8). In this case, the amount of **4d** could be decreased to only 1 mol% without any loss of the yield. This low loading of **4d** seems to be achieved due to its self-assembly and due to a hydrophobic effect of organic compounds in water.[10] As to secondary bromides, although α-bromopropionic acid esters (**1i**, **1j**) were poorly reactive (Table 3, entries 9 and 10), methyl α-bromophenylacetate (**1k**) gave a phenylglycine derivative (**3k**) in good yield (Table 3, entry 11).

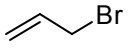
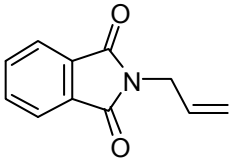
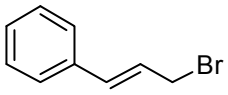
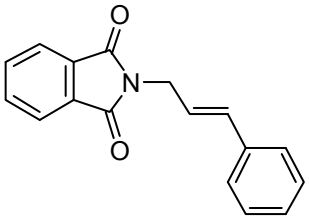
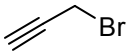
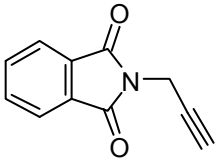
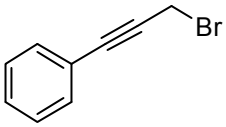
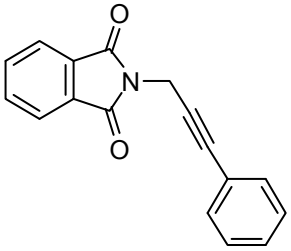
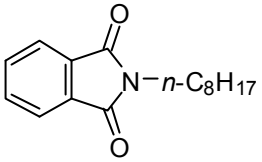
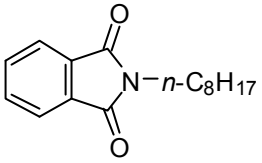
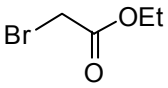
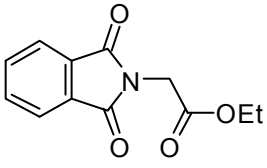
Then we investigated the reactions of various water-soluble anionic nucleophiles (**2b**–**2e**) with α-bromoesters (**1h**, **1k**) by using **4d** (Table 4). Sodium azide (**2b**) reacted with **1k** to give the product (**7a**) quantitatively, but didn't react with **1h** at all (Table 4, entries 1 and 2). Sodium benzenethiolate (**2c**) and sodium phenoxide (**2d**) reacted with both **1h** and **1k** to afford the corresponding products (**7b**–**7e**) in moderate to good yields (Table 4, entries 3–6). Although a harsher condition was required, a fluorination reaction of **1k** with cesium fluoride could also be performed to give the α-fluoroester (**7f**) in acceptable yield (Table 4, entry 7).

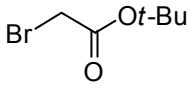
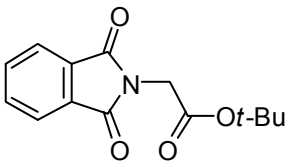
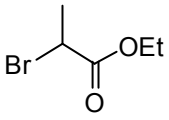
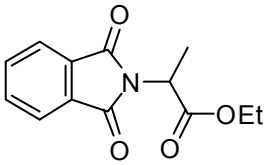
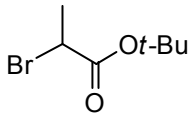
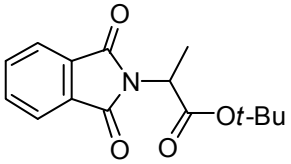
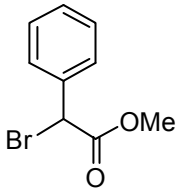
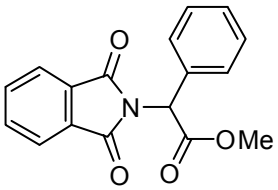


Scheme 2. Formation of a reaction medium by the self-assembly of **4d**

Table 3. Nucleophilic substitution reaction in water between various electrophiles (**1**) and **2a** in the presence of **4d**[a]

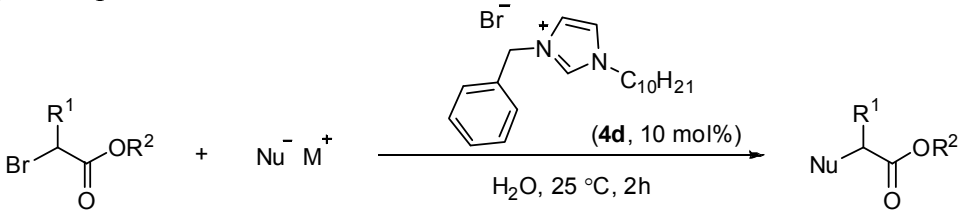


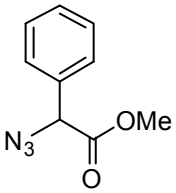
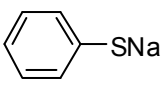
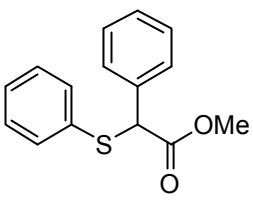
Entry	R—X (**1**)		Product (**3**)		Yield (%)[b]
1		(**1b**)		(**3b**)	28
2		(**1c**)		(**3c**)	60
3		(**1d**)		(**3d**)	55
4		(**1e**)		(**3e**)	82
5	*n*-C_8H_{17}Br	(**1f**)		(**3f**)	4
6	*n*-C_8H_{17}OMs	(**1f'**)		(**3f**)	16
7		(**1g**)		(**3g**)	77

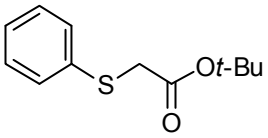
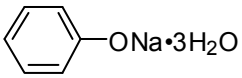
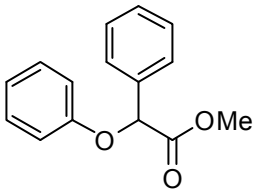
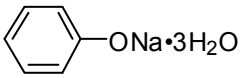
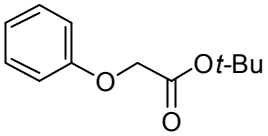
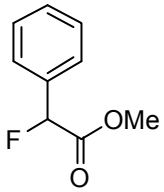
8[c]		(**1h**)		(**3h**)	>99
9		(**1i**)		(**3i**)	16
10		(**1j**)		(**3j**)	10
11		(**1k**)		(**3k**)	70

[a] **1** (0.5 mmol), **2a** (0.6 mmol), **4d** (0.05 mmol), and H_2O (5.0 mmol) were used for the reaction.
[b] Isolated yields.
[c] The reaction was performed using 1 mol% of **4d** (0.005 mmol).

Table 4. Nucleophilic substitution reaction in water between α-bromoesters (**1h**, **1k**) and various nucleophiles (**2**) in the presence of **4d**[a]



Entry	Nucleophile (**2**)		R^1	R^2	(**1**)	Product (**7**)		Yield (%)[b]
1	NaN_3	(**2b**)	Ph	Me	**1k**		(**7a**)	>99
2	NaN_3	(**2b**)	H	*t*-Bu	**1h**	–		0
3		(**2c**)	Ph	Me	**1k**		(**7b**)	47

4		(**2c**)	H	*t*-Bu	**1h**		(**7c**)	40
5		(**2d**)	Ph	Me	**1k**		(**7d**)	85
6		(**2d**)	H	*t*-Bu	**1h**		(**7e**)	93
7[c]	CsF	(**2e**)	Ph	Me	**1k**		(**7f**)	53

[a] **1** (0.5 mmol), **2** (0.6 mmol), **4d** (0.05 mmol), and H_2O (5.0 mmol) were used for the reaction.
[b] Isolated yields.
[c] The reaction was performed at 100 ºC for 3h.

In conclusion, we showed the usefulness of an imidazolium salt in water for construction of a reaction medium working as an ionic liquid. It assembled in water efficiently to form an interfacial medium in which nucleophilic substitution reactions took place. Furthermore, the hydrophobic effect of organic compounds might promote the reaction. These results suggest a new reaction medium. Further studies on the design of the imidazolium salt for higher efficiency are currently under investigation in our laboratory.

EXPERIMENTAL

Instrumentation and Chemicals

Nuclear magnetic resonance spectra were taken on a Varian UNITY INOVA 500 (^{1}H, 500 MHz; ^{13}C, 125.7 MHz) spectrometer using tetramethylsilane for ^{1}H NMR as an internal standard (δ = 0 ppm) and $CDCl_3$ for ^{13}C NMR as an internal standard (δ = 77.0 ppm). ^{1}H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sext = sextet, sept = septet, br = broad, m = multiplet), coupling constants (Hz), integration. ^{19}F NMR spectra were measured on a Varian Mercury 200 (^{19}F, 188 MHz) spectrometer with hexafluorobenzene as an internal standard (δ = 0 ppm). GC-MS analyses and High-resolution mass spectra were obtained with a JEOL JMS-700 spectrometer by electron ionization at 70 eV. Infrared spectra (IR) spectra were determined on a SHIMADZU FTIR-8200PC spectrometer. Melting points were

determined using a YANAKO MP-500D.

Flash column chromatography was carried out using Kanto Chemical silica gel (spherical, 40–50 μm). Unless otherwise noted, commercially available reagents were used without purification.

Experimental Procedure

***General procedure of nucleophilic substitution reactions between alkyl halides and anionic nucleophiles*:**

To a 5 mL vial, alkyl halide (**1**, 0.5 mmol), nucleophile (**2**, 0.6 mmol), imidazolium salt (**4d**, 0.05 mmol), and water (5.0 mmol) were added one by one. The mixture was stirred for 2 h in an oil bath kept at 25 °C. After stirring, the mixture was diluted with EtOAc and dried with anhydrous sodium sulfate. Then it was concentrated in vacuo. Purification by flash silica gel column chromatography using hexane/ EtOAc as an eluent gave the corresponding products.

Procedure for preparation of imidazolium salts:

1-Hexadecyl-3-phenylmethyl-1*H*-imidazolium bromide (4a): A mixture of 1-hexadecyl-1*H*-imidazole (0.50 mmol, 0.015 g) and benzyl bromide (0.60 mmol, 0.071 mL) was heated to 100 ºC for 2 h. After cooling to room temperature, the resulting solid was collected and washed with cooled Et_2O to give 1-hexadecyl-3-phenylmethyl-1*H*-imidazolium bromide (**4a**) as a white solid (0.23 g, 99%): ^{1}H NMR ($CDCl_3$) δ 10.87 (m, 1H), 7.49 (m, 2H), 7.39 (m, 3H), 7.21 (m, 2H), 5.63 (s, 2H), 4.29 (t, *J* = 7.5 Hz, 2H), 1.91 (tt, *J* = 7.0 Hz, 7.0 Hz, 2H), 1.31 (m, 4H), 1.29–1.20 (m, 22H), 0.87 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 137.6, 132.9, 129.55, 129.47, 129.1, 121.5, 53.4, 50.3, 31.9, 30.2, 29.67, 29.66, 29.65, 29.62, 29.61, 29.55, 29.4, 29.3, 28.9, 26.3, 22.7, 14.1. IR (KBr): 3437, 3080, 2916, 2851, 1560, 1472, 1368, 1327, 1148, 837, 824, 735, 712, 679, 617 cm^{-1}. HRMS Calcd for $C_{26}H_{43}N_2$: $2M^+$+Br^-, 845.6030. Found: m/z 845.6036. Anal. Calcd for $C_{26}H_{43}BrN_2$: C, 67.37; H, 9.35. Found: C, 67.29; H, 9.09. Mp 74.5–75.1 °C.

1-Methyl-3-phenylmethyl-1*H*-imidazolium bromide (4b): A mixture of 1-methyl-1*H*-imidazole (2.0 mmol, 0.16 g) and benzyl bromide (2.1 mmol, 0.25 mL) was heated to 100 ºC for 2 h. After cooling to room temperature, 2 mL of Et_2O were added, the mixture was refluxed, and the supernatant liquid was decanted off. After these procedures were repeated several times, the residue was vacuumed under a reduced pressure to give 1-methyl-3-phenylmethyl-1*H*-imidazolium bromide (**4b**) as a purple oil (0.51 g, 100%): CAS RN [65039-11-4] ^{1}H NMR ($CDCl_3$) δ 10.37 (s, 1H), 7.47 (m, 3H), 7.37–7.32 (m, 4H), 5.56 (s, 2H), 4.04 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 137.3, 132.9, 129.5, 129.4, 129.0, 123.5, 121.8, 53.3, 36.7.

1-Butyl-3-phenylmethyl-1*H*-imidazolium bromide (4c): A mixture of 1-butyl-1*H*-imidazole (2.0 mmol, 0.25 g) and benzyl bromide (2.1 mmol, 0.25 mL) was heated to 100 ºC for 2 h. After cooling to room temperature, 2 mL of Et_2O were added, the mixture was refluxed, and the supernatant liquid was decanted off. After these procedures were repeated several times, the residue was vacuumed under a reduced pressure to give 1-butyl-3-phenylmethyl-1*H*-imidazolium bromide (**4c**) as an orange oil (0.61 g, 100%): CAS RN [642096-86-4] ^{1}H NMR ($CDCl_3$) δ 10.56 (s, 1H), 7.48 (m, 2H), 7.43 (t, *J* = 1.5 Hz, 1H), 7.39 (t, *J* = 1.5 Hz, 1H), 7.36–7.30 (m, 3H), 5.59 (s, 2H), 4.27 (t, *J* = 7.5 Hz, 2H), 1.86 (m, 2H), 1.33 (m, 2H), 0.90 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 136.8, 133.1, 129.4, 129.3, 128.9, 122.1, 121.9, 53.1, 49.8, 32.0, 19.4, 13.3.

1-Decyl-3-phenylmethyl-1*H*-imidazolium bromide (4d): A mixture of 1-decyl-1*H*-imidazole (1.2 mmol, 0.25 g) and benzyl bromide (1.3 mmol, 0.16 mL) was heated to 100 ºC for 2 h. After cooling to room temperature, 2 mL of Et_2O were added, the mixture was refluxed, and the supernatant liquid was decanted off. After these procedures were repeated several times, the residue was vacuumed under a reduced pressure to give 1-decyl-3-phenylmethyl-1*H*-imidazolium bromide (**4d**) as a white solid (0.47 g, 100%): ^{1}H NMR ($CDCl_3$) δ 10.87 (s, 1H), 7.48 (m, 2H), 7.41–7.37 (m, 3H), 7.23 (m, 2H), 5.62 (s, 2H), 4.28 (t, *J* = 7.5 Hz, 2H), 1.90 (tt, *J* = 7.5 Hz, 7.5 Hz, 2H), 1.36–1.18 (m, 14H), 0.87 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 137.5, 132.9, 129.54, 129.45, 129.1, 121.5, 53.4, 50.3, 31.8, 30.2, 29.4, 29.3, 29.2, 28.9, 26.2, 22.6, 14.1. IR (KBr): 3439, 3067, 2924, 2855, 1624, 1560, 1497, 1456, 1362, 1157, 712 cm^{-1}. HRMS Calcd for $C_{20}H_{31}N_2$: $2M^+$+Br^-, 677.4152. Found: *m*/*z* 677.4144. Mp 34–35 °C (deliquescent material).

1-Decyl-3-cyclohexylmethyl-1*H*-imidazolium bromide (5): A mixture of 1-decyl-1*H*-imidazole (0.5 mmol, 0.10 g) and bromomethylcyclohexane (0.51 mmol, 0.071 mL) was heated to 100 ºC for 12 h. After cooling to room temperature, 2 mL of Et_2O were added, the mixture was refluxed, and the supernatant liquid was decanted off. After these procedures were repeated several times, the residue was vacuumed under a reduced pressure to give 1-decyl-3-cyclohexylmethyl-1*H*-imidazolium bromide (**5**) as a colorless oil (0.20 g, 100%): ^{1}H NMR ($CDCl_3$) δ 10.74 (s, 1H), 7.27 (t, *J* = 2.0 Hz, 1H), 7.23 (t, *J* = 2.0 Hz, 1H), 4.36 (t, *J* = 7.5 Hz, 2H), 4.20 (d, *J* = 7.5 Hz, 2H), 1.95–1.81 (m, 3H), 1.75 (m, 2H), 1.67 (m, 2H), 1.62 (m, 2H), 1.32 (m, 4H), 1.29–1.11(m, 14H), 1.05 (dq, *J* = 3.0 Hz, 12.0 Hz, 2H), 0.86 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 138.1, 122.0, 121.2, 55.9, 50.1, 38.5, 31.8, 30.3, 30.0, 29.4, 29.3, 29.2, 28.9, 26.2, 25.7, 25.3, 22.6, 14.1. IR (neat): 3431, 3059, 2924, 2853, 1560, 1451, 1375, 1165, 779, 644 cm^{-1}. HRMS Calcd for $C_{20}H_{37}N_2$: $2M^+$+Br^-, 689.5091. Found: *m*/*z* 689.5119.

1-Decyl-3-methyl-1*H*-imidazolium bromide (6a): A mixture of 1-methyl-1*H*-imidazole (2.1 mmol, 0.17 mL) and 1-boromodecane (2.0 mmol, 0.44 g) was heated to 100 ºC for 12 h. After cooling to room temperature, 2 mL of Et_2O were added, the mixture was refluxed, and the supernatant liquid was decanted off. After these procedures were repeated several times, the residue was vacuumed under a reduced pressure to give 1-decyl-3-methyl-1*H*-imidazolium bromide (**6a**) as a colorless oil (0.61 g, 100%): CAS RN [188589-32-4] ^{1}H NMR ($CDCl_3$) δ 10.39 (d, *J* = 6.5 Hz, 1H), 7.55 (m, 1H), 7.38 (m, 1H), 4.28 (t, *J* = 7.5 Hz, 2H), 4.10 (s, 3H), 1.88 (tt, *J* = 7.5 Hz, 7.5 Hz, 2H), 1.35–1.15 (m, 14H), 0.84 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 137.4, 123.5, 121.7, 50.1, 36.7, 31.7, 30.2, 29.33, 29.26, 29.1, 28.9, 26.2, 22.5, 14.0.

1-Hexadecyl-3-methyl-1*H*-imidazolium bromide (6b): A mixture of 1-methyl-1*H*-imidazole (11 mmol, 0.84 mL) and 1-boromohexadecane (10 mmol, 3.1 g) was heated to 100 ºC for 21 h. Then 10 mL of Et_2O were added to the resulting mixture, and the mixture was refluxed. After cooling to room temperature, the precipitate was collected and washed with cooled Et_2O to give 1-hexadecyl-3-methyl-1*H*-imidazolium bromide (**6b**) as a white solid (3.9 g, 100%): CAS RN [132361-22-9] ^{1}H NMR ($CDCl_3$) δ 10.41 (s, 1H), 7.34 (t, *J* = 2.0 Hz, 1H), 7.25 (t, *J* = 2.0 Hz, 1H), 4.31 (t, *J* = 7.5 Hz, 2H), 4.12 (s, 3H), 1.90 (tt, *J* = 7.5 Hz, 7.5 Hz, 2H), 1.38–1.20 (m, 26H), 0.87 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 138.0, 123.1, 121.5, 50.3, 36.8, 31.9, 30.2, 29.7, 29.62, 29.61, 29.56, 29.5, 29.33, 29.32, 28.9, 26.2, 22.6, 14.1. Mp 62.0–63.0 °C.

Characterization Data of Products

2-(Phenylmethyl)-1*H*-isoindole-1,3(2*H*)-dione (3a): CAS RN [2142-01-0]

Yield: 96%, white solid. ^{1}H NMR ($CDCl_3$) δ 7.85 (m, 2H), 7.71 (m, 2H), 7.44 (m, 2H), 7.32 (m, 2H), 7.26 (m, 1H), 4.85 (s, 2H). ^{13}C NMR ($CDCl_3$) δ 168.0, 136.3, 134.0, 132.1, 128.7, 128.6, 127.8, 123.3, 41.6. Mp 114.7–115.2 °C.

2-(Prop-2-enyl)-1*H*-isoindole-1,3(2*H*)-dione (3b): CAS RN [5428-09-1]

Yield: 28%, white solid. ^{1}H NMR ($CDCl_3$) δ 7.86 (m, 2H), 7.72 (m, 2H), 5.89 (ddt, *J* = 17.0 Hz, 10.5 Hz, 5.5 Hz, 1H), 5.25 (ddt, *J* = 17.0 Hz, 1.0 Hz, 1.5 Hz, 1H), 5.20 (ddt, *J* = 10.5 Hz, 1.0 Hz, 1.5 Hz, 1H), 4.30 (ddd, *J* = 5.5 Hz, 1.5 Hz, 1.5 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 167.9, 134.0, 132.1, 131.5, 123.3, 117.7, 40.0. Mp 64.8–65.1 °C.

2-[(2*E*)-3-phenylprop-2-enyl]-1*H*-isoindole-1,3(2*H*)-dione (3c): CAS RN [17480-07-8]

Yield: 60%, white solid. ^{1}H NMR ($CDCl_3$) δ 7.87 (m, 2H), 7.72 (m, 2H), 7.35 (m, 2H), 7.28 (m, 2H), 7.22 (m, 1H), 6.66 (d, *J* = 16.0 Hz, 1H), 6.26 (dt, *J* = 16.0 Hz, 6.5 Hz, 1H), 4.45 (dd, *J* = 6.5 Hz, 1.0 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 168.0, 136.3, 134.0, 133.8, 132.2, 128.5, 127.9, 126.5, 123.3, 122.7,

39.7. Mp 150.5–151.2 °C.

2-(Prop-2-ynyl)-1*H*-isoindole-1,3(2*H*)-dione (3d): CAS RN [7223-50-9]

Yield: 55%, white solid. ^{1}H NMR ($CDCl_3$) δ 7.89 (m, 2H), 7.74 (m, 2H), 4.46 (d, *J* = 2.5 Hz, 2H), 2.22 (t, *J* = 2.5 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 167.0, 134.2, 132.0, 123.6, 77.2, 71.5, 27.0. Mp 149.0–149.9 °C.

2-(3-Phenylprop-2-ynyl)-1*H*-isoindole-1,3(2*H*)-dione (3e): CAS RN [4656-94-4]

Yield: 82%, white solid. ^{1}H NMR ($CDCl_3$) δ 7.90 (m, 2H), 7.74 (m, 2H), 7.42 (m, 2H), 7.31–7.25 (m, 3H), 4.68 (s, 2H). ^{13}C NMR ($CDCl_3$) δ 167.1, 134.2, 132.1, 131.9, 128.5, 128.2, 123.5, 122.3, 83.0, 82.6, 27.9. Mp 149.0–150.0 °C.

2-Octyl-1*H*-isoindole-1,3(2*H*)-dione (3f): CAS RN [59333-62-9]

Yield: 16%, white solid. ^{1}H NMR ($CDCl_3$) δ 7.83 (m, 2H), 7.70 (m, 2H), 3.67 (t, *J* = 7.5 Hz, 1H), 1.66 (tt, *J* = 7.5 Hz, 7.5 Hz, 2H), 1.37–1.20 (m, 10H), 0.86 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 168.5, 133.8, 132.2, 123.1, 38.1, 31.8, 29.1, 28.6, 26.9, 22.6, 14.0. Mp 45.5–46.0 °C.

Ethyl 2-(1,3-dioxoisoindolin-2-yl)acetate (3g): CAS RN [6974-10-3]

Yield: 77%, white solid. ^{1}H NMR ($CDCl_3$) δ 7.89 (m, 2H), 7.75 (m, 2H), 4.44 (s, 2H), 4.23 (q, *J* = 7.0 Hz, 2H), 1.29 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 167.5, 167.2, 134.2, 132.0, 123.6, 61.9, 38.9, 14.1. Mp 112.0–112.5 °C.

***tert*-Butyl 2-(1,3-dioxoisoindolin-2-yl)acetate (3h)**: CAS RN [6297-93-4]

Yield: >99%, white solid. ^{1}H NMR ($CDCl_3$) δ 7.88 (m, 2H), 7.74 (m, 2H), 4.34 (s, 2H), 1.46 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 167.6, 166.3, 134.1, 132.1, 123.5, 82.8, 39.7, 28.0. Mp 96.0–96.8 °C.

Ethyl 2-(1,3-dioxoisoindolin-2-yl)propanoate (3i): CAS RN [14380-86-0]

Yield: 16%, white solid. ^{1}H NMR ($CDCl_3$) δ 7.86 (m, 2H), 7.73 (m, 2H), 4.96 (q, *J* = 7.5 Hz, 1H), 4.20 (m, 2H), 1.69 (d, *J* = 7.5 Hz, 3H), 1.23 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (CDCl3) δ 169.7, 167.4, 134.1, 131.9, 123.4, 61.8, 47.5, 15.2, 14.1. Mp 61.5–62.5 °C.

***tert*-Butyl 2-(1,3-dioxoisoindolin-2-yl)propanoate (3j)**: CAS RN [76517-88-9]

Yield: 10%, white solid. ^{1}H NMR ($CDCl_3$) δ 7.86 (m, 2H), 7.73 (m, 2H), 4.87 (q, *J* = 7.5 Hz, 1H), 1.65 (d, *J* = 7.5 Hz, 3H), 1.42 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 168.7, 167.6, 134.0, 131.9, 123.4, 82.3, 48.3, 27.8, 15.3. Mp 95.2–96.0 °C.

Methyl 2-(1,3-dioxoisoindolin-2-yl)-2-phenylacetate (3k): CAS RN [1082222-36-3]

Yield: 70%, white solid. ^{1}H NMR ($CDCl_3$) δ 7.86 (m, 2H), 7.72 (m, 2H), 7.55 (m, 2H), 7.35 (m, 3H), 6.02 (s, 1H), 3.81(s, 3H). ^{13}C NMR ($CDCl_3$) δ 168.5, 167.1, 134.4, 134.2, 131.8, 129.7, 128.63, 128.56, 123.6, 55.8, 53.1. Mp 102.5–103.0 °C.

Methyl 2-azido-2-phenylacetate (7a): CAS RN [409335-57-5]

Yield: >99%, pale yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.41 (m, 5H), 4.98 (s, 1H), 3.78 (s, 3H). ^{13}C

NMR ($CDCl_3$) δ 169.6, 133.8, 129.3, 129.1, 127.6, 65.3, 52.9.

Methyl 2-phenyl-2-(phenylthio)acetate (7b): CAS RN [51256-38-3]

Yield: 47%, white solid. ^{1}H NMR ($CDCl_3$) δ 7.61 (m, 3H), 7.43 (m, 2H), 7.37 (m, 1H), 7.33 (m, 2H), 7.29 (m, 2H), 5.11 (s, 1H), 3.77 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 165.3, 136.2, 134.2, 130.2, 129.9, 129.7, 128.6, 128.5, 127.8, 75.2, 53.2. Mp 108.0–109.0 °C.

***tert*-Butyl 2-(phenylthio)acetate (7c)**: CAS RN [63006-68-8]

Yield: 40%, colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.95 (m, 2H), 7.68 (m, 1H), 7.58 (m, 2H), 4.04 (s, 2H), 1.36 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 161.2, 139.0, 134.1, 129.1, 128.5, 83.6, 62.1, 27.7.

Methyl 2-phenoxy-2-phenylacetate (7d): CAS RN [32191-46-1]

Yield: 85%, colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.58 (m, 2H), 7.39 (m, 3H), 7.28 (m, 2H), 6.98 (tt, J = 7.5 Hz, 1.0 Hz, 1H), 6.95 (m, 2H), 5.65 (s, 1H), 3.74 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 170.4, 157.3, 135.4, 129.6, 129.0, 128.8, 127.1, 121.8, 115.5, 78.6, 52.6.

***tert*-Butyl 2-phenoxyacetate (7e)**: CAS RN [36304-22-0]

Yield: 93%, colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.29 (m, 2H), 6.98 (tt, J = 7.5 Hz, 1.0 Hz, 1H), 6.90 (m, 2H), 4.52 (s, 2H), 1.49 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 168.1, 157.9, 129.5, 121.5, 114.6, 82.3, 65.7, 28.0.

Methyl 2-fluoro-2-phenylacetate (7f): CAS RN [17841-30-4]

Yield: 53%, colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.46 (m, 2H), 7.41 (m, 3H), 5.80 (d, J = 47.5 Hz, 1H), 3.79 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 169.0 (d, J = 27.8 Hz), 134.1 (d, J = 20.6 Hz), 129.7 (d, J = 2.0 Hz), 128.8, 126.7 (d, J = 6.2 Hz), 89.3 (d, J = 185.7 Hz), 52.6. ^{19}F NMR ($CDCl_3$) δ –18.1.

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